Systematic Review and Meta-Analysis

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Adjuvant chemotherapy improves oncological outcomes of resectable intrahepatic cholangiocarcinoma

A meta-analysis

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Abstract

Objective: To define the role of adjuvant chemotherapy in the management of resectable intrahepatic cholangiocarcinoma (ICC) by performing a meta-analysis.

Summary background data: Oncological benefit of adjuvant chemotherapy in resectable ICC remains controversial, high-level evidence in such context is lacking.

Method: A comprehensive search using Pubmed, EMbase, and Web of Science was performed from inception to October 2018. Studies compared the survival of patients receiving adjuvant chemotherapy versus surgery alone were included. Data were analyzed using random effect model. Quality of each study and presence of publication bias were assessed by Newcastle–Ottawa score (NOS) and funnel plot with Egger test respectively.

Results: The present meta-analysis included 15 studies (all were retrospective series) and 5060 patients. Adjuvant chemotherapy was administered either intravenously or intra-arterially in the form of trans-arterial chemo-embolization (TACE). The average NOS for the included studies was 6.5. Pooled analysis of the included studies demonstrated significant advantage in the adjuvant chemotherapy group (HR 0.66, 0.55–079, $P<.001$, I-square [I^2]=20.8%). After 2 studies were removed for heterogeneity, advantage of adjuvant chemotherapy remained (HR 0.72, 0.62–0.84, $P<.001$, $I^2=0\%$). Funnel plot suggested no significant publication bias (Egger test, 2-tailed $P=.203$). Subgroup analyses suggested that intravenous route of chemotherapy injection ($P<.001$) and use of gemcitabine base regimen ($P=.004$) are associated with improved overall survival. Adjuvant chemotherapy did not improve disease-free survival in subgroup analysis ($P=.94$).

Conclusion: Adjuvant chemotherapy is associated with improved overall survival and should be considered in patients with ICC following curative resection and in particular to patients with advance disease.

Abbreviations: 5-FU = 5-fluorouracil, 95% CI = 95% confidence interval, HR = hazard ratio, I^2 = I-square, ICC = intrahepatic cholangiocarcinoma, NOS = Newcastle-Ottawa score, TACE = trans-arterial chemoembolization.

Keywords: adjuvant chemotherapy, intrahepatic cholangiocarcinoma, meta-analysis, oncological outcomes

Key Points

- Survivals of ICC were poor even after surgical resection of the tumor, routine adjuvant chemotherapy remained controversial
- This meta-analysis focused only on ICC which avoid contamination of results by other biliary tract cancers such as Klaskin and carcinoma of common bile duct
- Adjuvant chemotherapy was associated with improved overall survivals

1. Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy after hepatocellular carcinoma (HCC), it contributes to around 10% of all primary liver cancers.[1] Being a member of the cholangiocarcinoma

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family, it is considered a distinct disease entity with different pattern of tumor spread and prognosis when compared to cholangiocarcinoma arising from other parts of the biliary system. Unresectable ICC has a grave prognosis with median survival of only 6 to 9 months.[2–4] Complete resection is the only hope of long-term cure, however, the 5-year overall survival of patients after hepatectomy were around 30%.[5–7] This suboptimal oncological outcome sets the stage for studies focusing on factors that can improve long-term survival of the post-hepatectomy patients. Modification of surgical techniques such as radical lymphadenectomy[8–10] and wide resection margin[11,12] had been investigated in some studies, however, the influence of adjuvant chemotherapy on overall survival of resectable ICC remains poorly understood.[13–15] Due to its rarity, there have been no randomized or prospective study comparing the survival outcomes of adjuvant chemotherapy and surgery alone in this context. Furthermore, many of the published series were small retrospective cohort containing a mixture of patients with ICC, peri-hilar, and extrahepatic bile duct cancers with variable resection margin status (i.e., R0, R1, and R2).[16] A well-conducted meta-analysis is required to better analyze the role of adjuvant chemotherapy in resectable ICC. To the best of our knowledge, this is the first meta-analysis investigating the effect of adjuvant chemotherapy on overall survival in patients with resectable ICC.

2. Method

2.1. Search strategy, selection criteria, and data extraction

Systematic literature review was performed to identify articles that are relevant to the present study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A study was regarded as suitable for inclusion if the survival outcome (overall or disease-free survival) between surgery alone group and adjuvant therapy group patients (curative surgery followed by systemic intravenous or trans-arterial chemo-embolization (TACE)) were reported. Mesh terms including [intrahepatic], [cholangiocarcinoma], and [adjuvant] were used for literature search and only articles written in English were extracted using PUBMED, EMBASE, and WEB OF SCIENCE from inception to October 2018.

Approval from Institutional Review Board (IRB) for performing this meta-analysis was not required in our center as it did not involve patients from our locality. The research protocol of the present study has not been registered.

2.2. Search criteria

Two authors (MKW and LB) performed literature search independently. Study was excluded if there was presence of any one of the following conditions:

1) Outcome data contamination by case-mix analysis of intrahepatic and extrahepatic cholangiocarcinoma, such as hilar cholangiocarcinoma (Klaskin tumor), carcinoma of common bile duct, or carcinoma of gallbladder;
2) Radiotherapy as the only adjuvant treatment;
3) Hepatectomy performed in palliative intent (i.e., gross tumorous involvement of resection margin or R2 resection;
4) Direct comparison between adjuvant chemotherapy and surgery alone group not performed,
5) Case number less than 5 in each treatment arm;
6) Hazard ratio (HR) and 95% confidence interval not available or deducible;
7) Review article, conference abstract, and case report.

In addition, we carefully checked the source and period of data collection so as to exclude duplicated data. All the references of the eligible studies were manually checked to avoid missing of relevant papers in the analysis. When different published articles shared part or all of a single data source, we included only the most up-to-date and relevant article.

2.3. Data extraction

Name of first author, country of origin, sample size, study population characteristics, modality of adjuvant treatment, chemotherapeutic regimen, HR with 95% CI of overall and disease-free survivals, and median follow-up duration was extracted from the included studies. When HR and 95% CI were not provided in the full-text, they were estimated using the provided survival data or estimated from the Kaplan–Meier curves using the methods described by Tierney et al.[17] If survival data were provided from both unmatched and matched population in the same article, data from the matched comparison were used for pooled analysis. Discrepancies between reviewers (MKW and LB) during data extraction were resolved by consensus as instructed by the senior author (CTT) of this study. Effort had been made to contact author of the published articles through email in case clarification or further data required.

2.4. Meta-analysis and assessment of publication bias

Meta-analysis was performed to find out the effect of adjuvant chemotherapy on survival after curative resection of ICC using random effect model. Significant heterogeneity was considered if I-square [I^2] value equals to 25% or above. Results of meta-analysis were presented by Forest plot. Degree of publication bias was presented by Funnel plot and assessed by Egger test. Significant publication bias was defined as P value below 0.05 (2-sided). Comprehensive Meta-Analysis (CMA) version 3.0 was used for statistical analyses in this study. The authors received no funding to conduct this study.

2.5. Assessment of individual study quality

Robustness of the included studies was evaluated by Newcastle–Ottawa Scale (NOS).[18] Score of 6 or above was regarded as satisfactory quality, while study with score 3 or below was regarded as low quality. Assessment was done by 2 authors (MKW and LB) independently. Discrepancy in assessment was resolved by consensus as per the senior author (CTT).

3. Results

3.1. Overview of the included studies

Initial search identified 1019 eligible studies. After excluding duplicates, 390 articles were screened using title and abstract content. An additional 376 articles were removed according to the exclusion criteria. Finally, 14 studies involving 5060 patients were filtered from the literature (Fig. 1). There was no randomized controlled trial found during the search. Among the 14 studies, 1 was an international multi-center,[19] 1 was a multi-center retrospective series,[20] 1 was a national study using national cancer database[21] and the rest were from single-center retrospective series. Included studies were originated from 3 different continents and 7 countries (Table 1): 4 studies were from the USA[21–24] and China,[25–29] 2 from Thailand,[30,31] 1 from

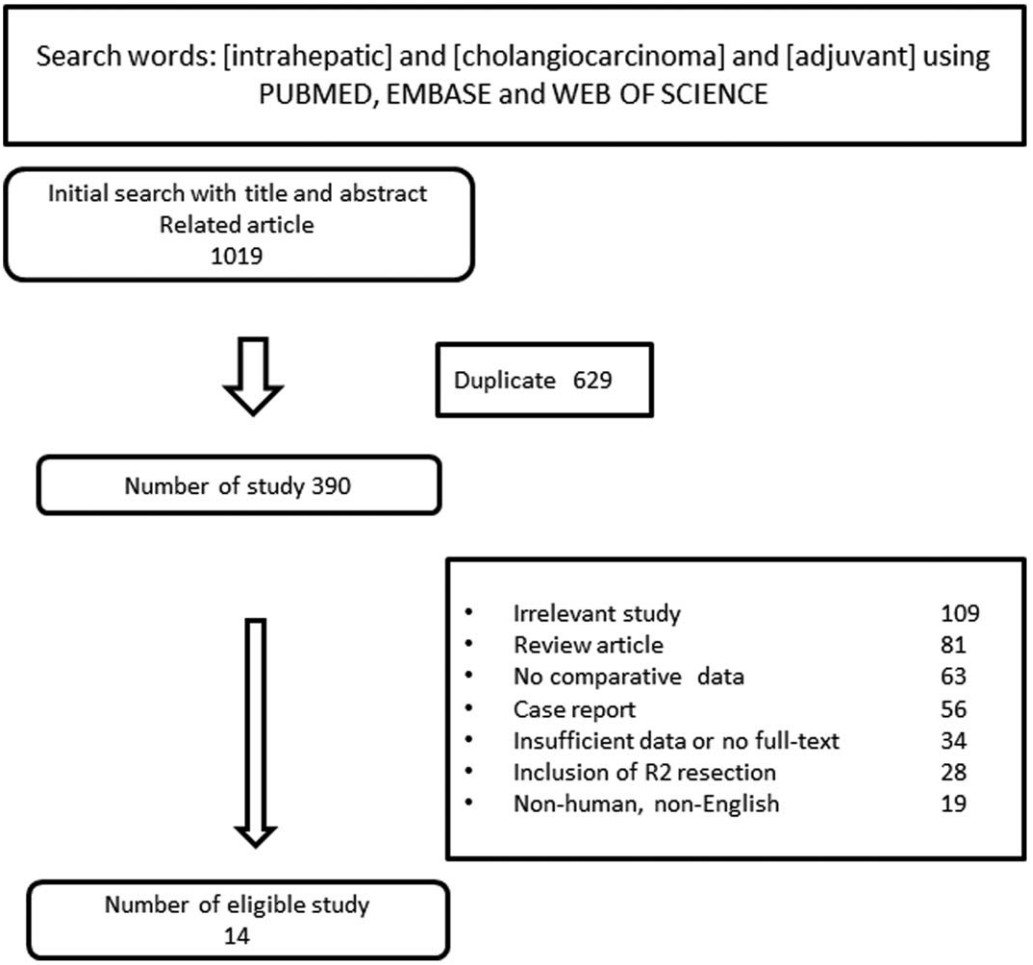

Figure 1. The search process and the number of papers excluded with reasons for exclusion.

Japan,[32] Germany,[33] Italy,[20] Korea,[34] and 1 international multicenter study[19] respectively. Demographic and tumor characteristics of the patient from each study were shown in Table 1. Attempts were made to contact the correspondence author of all included studies for further information but replies were received from 2 centers only.[30,32] Concerning the chemotherapeutic agents, 5-Fluorouracil and gemcitabine were the most commonly used in the included studies. The case number, follow-up duration, modes of chemotherapy and survival outcomes of each study were presented in Table 2.

Table 1

Background characteristics of the included studies.

Study (1st author)	Country	Yr	Study type	Study size	Sex, male%	Age	R0 resection margin, %	Node positive, %	T-size, cm	Multifocal tumor, %	VI, %
Roayaie S[21]	USA	1991–1997	RS	16	NS	62	68.8	NS	8	31.3	50
Bhudhisawasdi V[30]	Thailand	1998–2002	RS	171	67.8	56	40.9	NS	75.4% >4cm	39.2	84.8
Wu ZF[25]	China	2005–2006	RS	114	77.2	56	100	9.6	52.6% >5cm	30.7	12.3
Ribero D[19]	Italy	1990–2008	RM	434	56	65	88	26	6	32.3	48.6
Luvira V[29]	Thailand	2004–2009	RS	50	52	57.2	46	64	6.5	14	NS
Dhanasekaran R[23]	USA	2000–2009	RS	53	54.7	NS	75.5	24.5	49.1% >5cm	26.7	54.7
Miura JT[20]	USA	1998–2011	RN	1970	49.4	64	76.3	17.4	39.6% >5cm	NS	NS
Liu R[28]	China	2005–2011	RS	81	59	59	NS	61.7	NS	NS	NS
Li J[26]	China	2008–2011	RS	244	78.7	54	100	12.7	5.25	21.7	12.3
Li T[27]	China	2000–2011	RS	211	61.5	55	100	16.1	65.9% >5cm	18	23.7
Kim DH[33]	Korea	1995–2012	RS	215	64.2	60.2	92	27	5.1	17.7	30
Okumura S[31]	Japan	2004–2015	RS	109	61.5	68	83.5	29.4	4.2	23	63.3
Schweitzer N[32]	Germany	2000–2015	RS	50	NS	NS	NS	60	56% >7.33cm	NS	32
Doussot A[22]	USA	1993–2013	RS	189	29.7	65.4	80.4	11.1	6.9	28.6	36
Reames BN	international	1990–2015	RM	1154	55	60	87	17	71% >5cm	22	31

N-positive = nodal metastasis, RM = retrospective, multicenter, RN = retrospective, National database, RS = retrospective, single-center, VI = vascular invasion.

Table 2

Survival outcomes of the included studies.

Study (1st author)	Median FU (month)	Surgery alone gp, n	Adjuvant chemo gp, n	Route of adm	Chemo type	DFS (Sur vs adj)	HR	95% CI	OS (Sur vs adj) (month)	HR	95% CI	NOS
Roayaie S[21]	35.7	8	8	IV	5-FU	30.5:19.1	0.65	0.14–3.04	41.3:42.9	0.782	0.123–1.003	4
Bhudhisawasdi V[30]	NS	117	54	IV	5-FU,Mi-C	NS	NS	NS	NS	0.56	0.39–082	7
Wu ZF[25]	NS	57	57	IA	5-FU/CP,EPR,HCT	NS	NS	NS	10%:19% (5yr)	0.494	0.322–0.757	9
Ribero D[19]	36.5	318	116	NS	NS	NS	NS	NS	34.1%:33.1%(5yr)	0.99	0.72–1.37	7
Luvira V[29]	8	32	18	IV	5-FU based	4:7	0.61	0.32–1.18	7:13	0.61	0.32–1.18	4
Dhanasekaran R[23]	NS	32	21	NS	NS	NS	NS	NS	23.8:27.6	1.238	0.50–0.31	4
Miura JT[20]	NS	985	985	NS	NS	NS	NS	NS	24.8:23.1	0.88	0.74–1.06	6
Liu R[28]	NS	63	18	IA/IV	5-FU/CP/GEM/DOX/OX	NS	NS	NS	8:22	0.227	0.117–0.440	4
Li J[26]	25.3	122	122	IA	5-FU,EPR,HCT	15.7–22.0	0.97	0.66–1.42	23.2:27.6	1.07	0.66–1.73	6
Li T[27]	17	143	68	IA	5-FU,EPR,HCT	NS	1.69	1.09–1.25	NS	0.56	0.37–0.87	8
Kim DH[33]	NS	183	32	NS	5-FU /CP/GEM/OX	NS	NS	NS	NS	0.73	0.37–1.43	4
Okumura S[31]	NS	62	47	IV	GEM/S-1/both	NS	0.88	0.56–1.37	NS	0.66	0.38–1.11	7
Schweitzer N[32]	NS	25	25	IV	GEM,OS	NS	NS	NS	18:33.5	0.34	0.164–0.690	8
Doussot A[22]	42.5	138	51	both	GEM (IV),FLU (IA)	15:26.4	0.95	0.58–1.56	NS	NS	NS	7
Reames BN	NS	807	347	IV	GEM, platinum, 5-FU	NS	NS	NS	NS	0.6	0.49–0.74	7

95% CI = 95% confidence interval, CP = cisplatin, DFS = disease-free survival, DOX = doxorubicin, EPR = epirubicin, GEM = gemcitabine, HCT = hydroxycamptothecin, HR = hazard ratio, IA = intra-arterial,5-FU = 5-Fluorouracil, IV = intravenous, NOS = Newcastle–Ottawa Score, NS = not stated, OS = overall survival, OX = oxiloplatin.

3.2. Effect of adjuvant chemotherapy on overall survival

After extraction of HR and 95% CI from the 14 eligible studies, meta-analysis using random-effect model was performed. Superior overall survival for patients who had received adjuvant chemotherapy was demonstrated (HR 0.66, 0.55–079, $P < .001$, $I^2 = 20.8\%$) (Fig. 2). Two studies (Liu et al[29] and Schweitzer et al[33]) reported very large benefit from adjuvant chemotherapy (HR of 0.227 and 0.340 respectively), this was accounted for the relatively heterogeneity in the initial analysis ($I^2 = 21\%$). Analysis was repeated after excluding these 2 studies and the advantage of adjuvant chemotherapy still persisted (HR 0.72, 0.62–0.84, $P < .001$, $I^2 = 0\%$) (Fig. 3).

3.3. Subgroup analysis

3.3.1. Effect of route of chemotherapy administration on overall survival. The route of chemotherapy administration was described in 10 studies. Subgroup analysis was performed for studies in which chemotherapy was given via intravenous route.

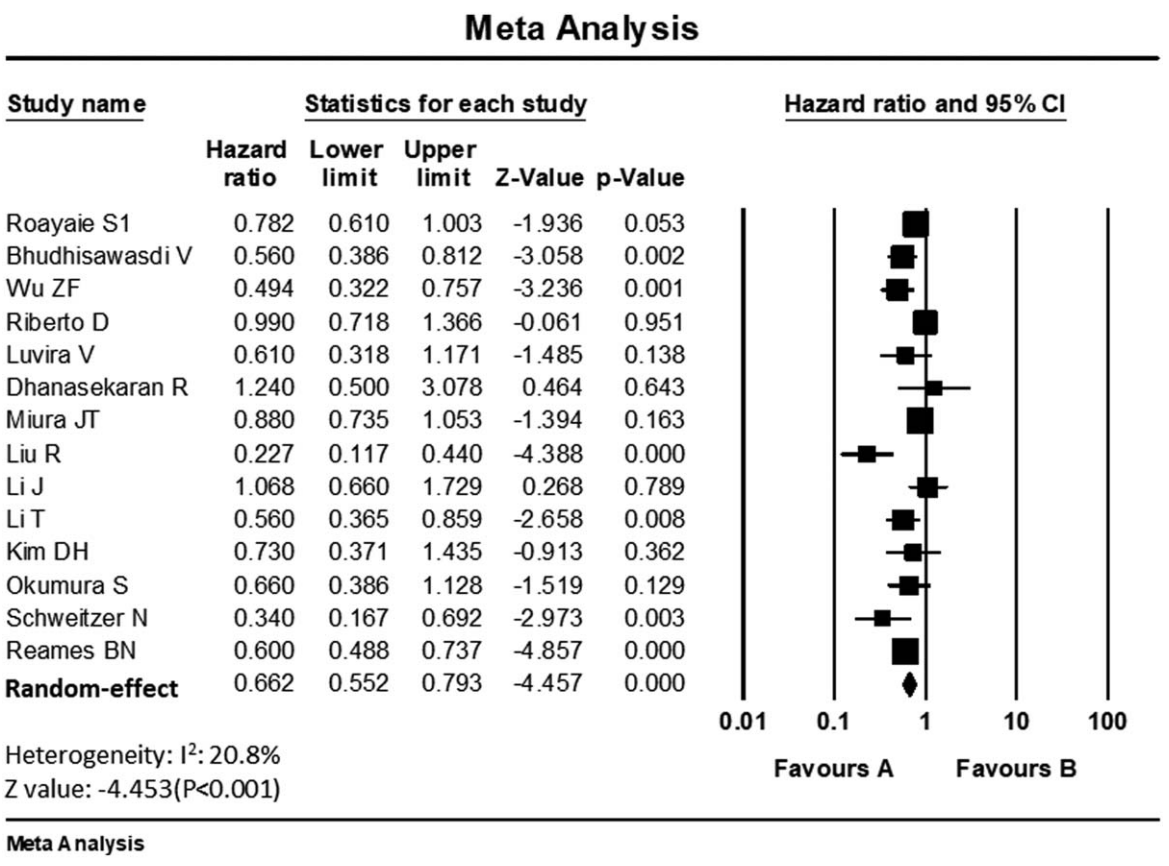

Figure 2. Forest plot illustrating the effect of adjuvant chemotherapy on overall survival.

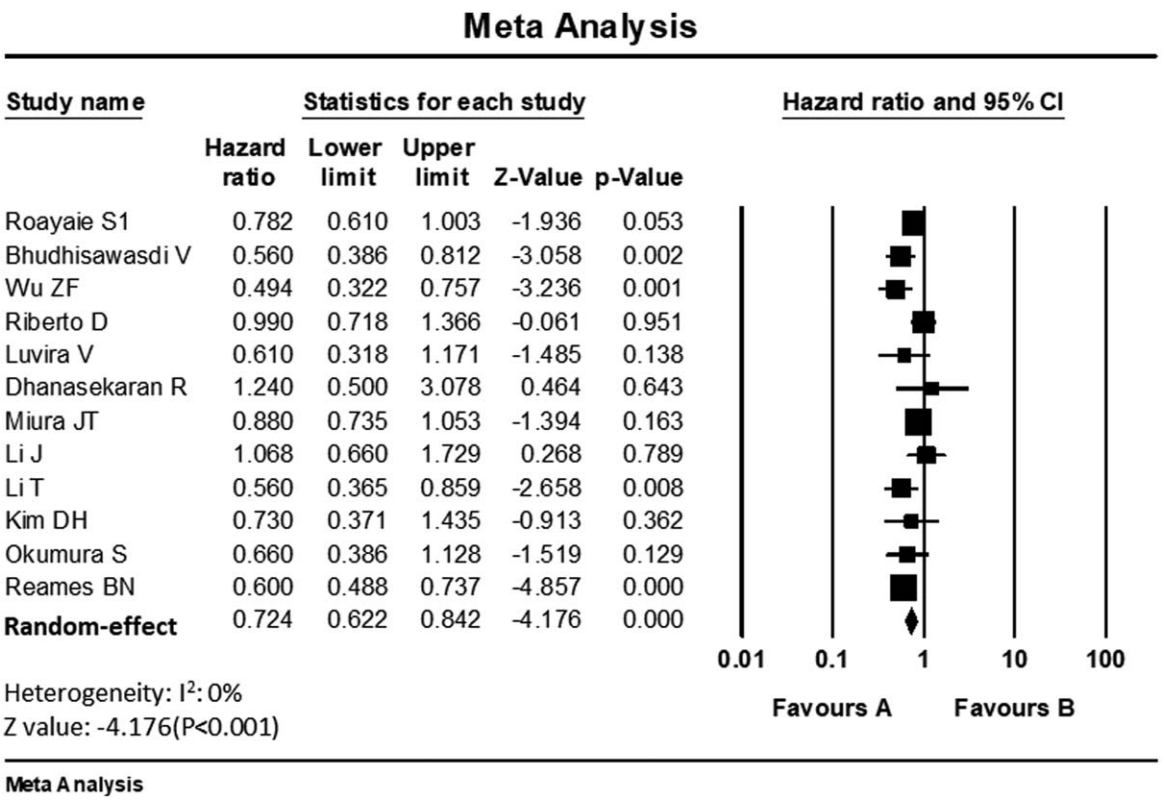

Figure 3. Forest plot illustrating the effect of adjuvant chemotherapy from individual study and overall result in random-effect model (2 studies removed).

Pooled analysis of the 5 studies suggested that intravenous chemotherapy was associated with improved overall survival (HR 0.621, 0.491–0.799, $I^2 = 0\%$, $P < .001$) (Fig. 4.). No significant survival benefit was demonstrated by the pooled analysis of the 4 studies using intra-arterial (TACE) adjuvant chemotherapy (HR 0.679, 0.313–1.469, $I^2 = 15\%$, $P = .325$) (Fig. 5)

3.3.2. Effect of using different chemotherapeutic agents on overall survival. The type of chemotherapeutic agent used for adjuvant treatment was described in 11 studies. There was no significant benefit associated with the use of 5-Fluorouracil (5-FU) based chemotherapy when compared with surgery alone (HR 0.782, 0.560–1.092, $I^2 = 12\%$, $P = .149$) (Fig. 6). However, significant survival benefit was shown in the pooled analysis of the 5 studies that incorporated gemcitabine in their chemotherapeutic regimen (HR 0.493, 0.339–0.715, $I^2 = 17.7\%$ $P < .001$) (Fig. 7).

3.3.3. Effect of adjuvant chemotherapy on disease-free survival. There were 6 studies reported the effect of adjuvant

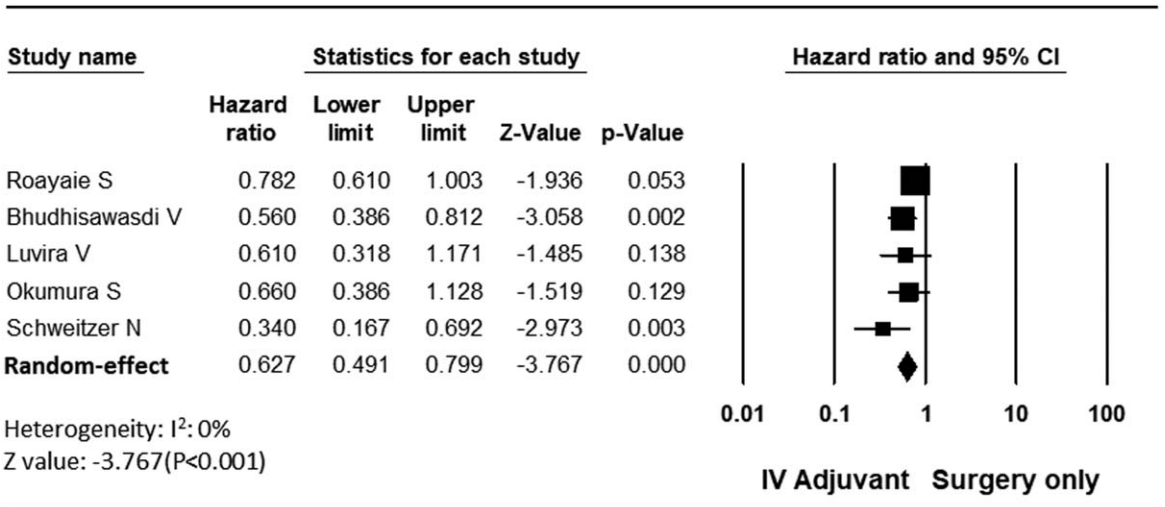

Figure 4. Subgroup analysis on the effect of intravenous adjuvant chemotherapy versus surgery alone group.

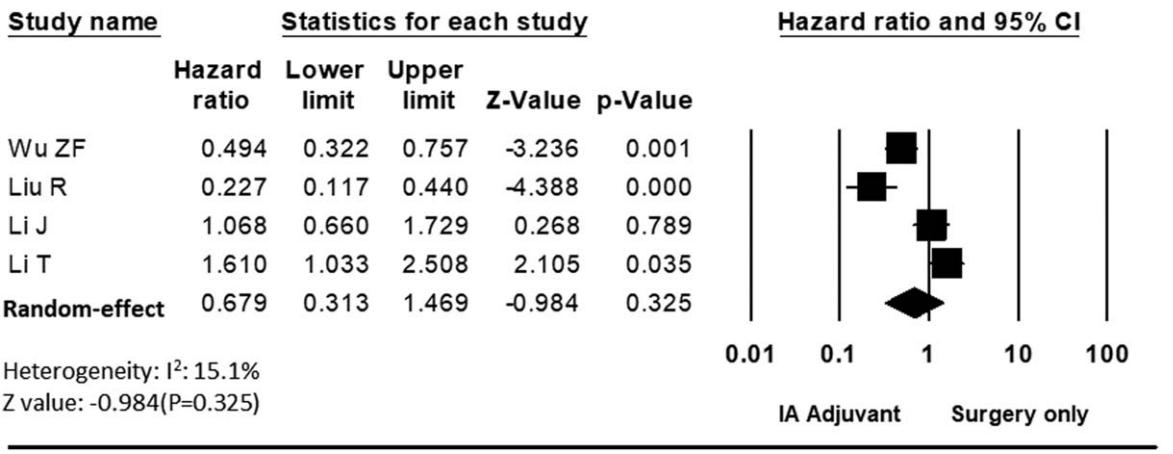

Figure 5. Subgroup analysis on the effect of intra-arterial adjuvant chemotherapy versus surgery alone group.

chemotherapy on disease-free survival. Most of the study did no show significant effect except 1 (Li et al[28]). Pooled analysis showed that adjuvant chemotherapy was not associated with benefit in disease-free survival (HR 0.99, 1.09–2.63, $I^2 = 0\%$, $P = .944$) (Fig. 8).

3.4. Assessment of publication bias

Publication bias was assessed by funnel plot and there was even distribution of the 14 studies on both side of the mean effect size (Fig. 9). Egger test suggested that there was no significant publication bias in the current meta-analysis ($P = .203$, 2-tailed, t value 1.36)

3.5. Assessment of the quality of the included studies

The overall quality of the included studies was satisfactory with mean NOS of 6.5. Majority of the studies achieved a good quality grading, ranging from NOS 6 to 8, mainly due to clear record of the patient's characteristic, exposure, and event documentation. None of the included studies received a poor NOS score, and 6 studies were graded as average (i.e., NOS of 4 out of 9) due to possible selection bias, significant confounders between the comparing groups and unclear documentation or insufficient follow-up duration (Table 3).

4. Discussion

The current meta-analysis concluded that use of adjuvant chemotherapy is associated improved overall survival when compared with surgery alone for patients with resectable ICC. Subgroup analyses suggested that intravenous chemotherapy administration and gemcitabine base adjuvant chemotherapy were associated with improved overall survival. However, TACE and 5-FU base adjuvant chemotherapy were not associated with survival benefit. No significant improvement was demonstrated in the use of adjuvant chemotherapy regarding disease-free survival. This study represents the first study to elucidate the effect of adjuvant chemotherapy in patients with resectable ICC using meta-analysis.

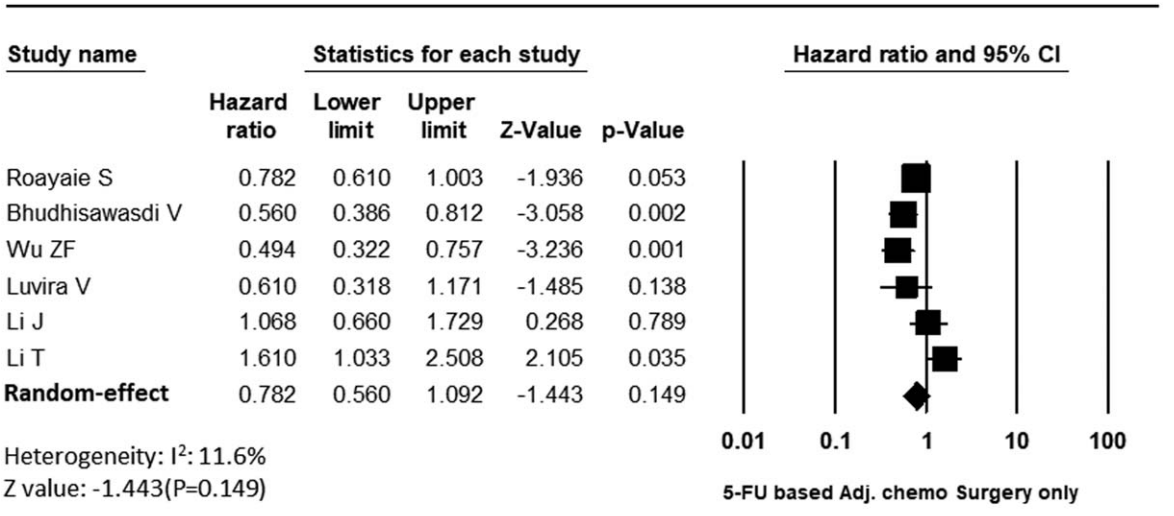

Figure 6. Subgroup analysis on the effect of using 5-FU based adjuvant chemotherapy versus surgery alone group.

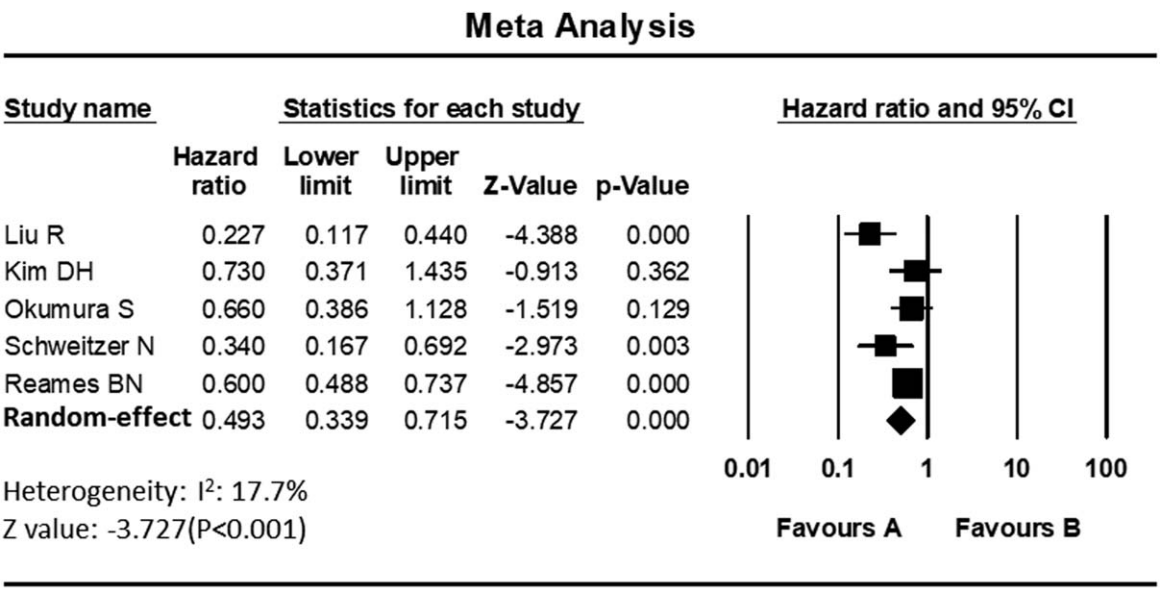

Figure 7. Subgroup analysis on the effect of using gemcitabine based adjuvant chemotherapy versus surgery alone group.

Survival benefit of adjuvant chemotherapy as illustrated in the meta-analysis of 14 studies was significantly contributed by the study from Schweitzer et al and Liu et al. Their disproportionately low HRs were related to a more advance disease stage in these 2 study populations as reflected by the high percentage of nodal involvement (i.e., over 60%). For the sake of reducing heterogeneity, these 2 studies were excluded and the benefit of adjuvant chemotherapy still remained, though to a lesser extent, suggesting that the beneficial effect of adjuvant chemotherapy might be more pronounced in node-positive ICC patients. Yet, this statement requires further studies to confirm.

Due to the intrinsic inflammatory mediating property of cholangiocyte, cholangiocarcinoma is inherently a chemo-resistant cancer.[35,36] With the development of chemotherapeutic agents, there was a significant improvement in the response rate of up to 30% to 50% after switching the first-line chemotherapeutic agent from 5-FU to gemcitabine.[37–39] Because of the lower response rate of ICC to 5-FU base chemotherapy, a much larger sample size is required to demonstrate the survival benefit of adjuvant chemotherapy using 5-FU, and that explains the negative finding of the subgroup analysis of 5-FU base chemotherapy in this study. A

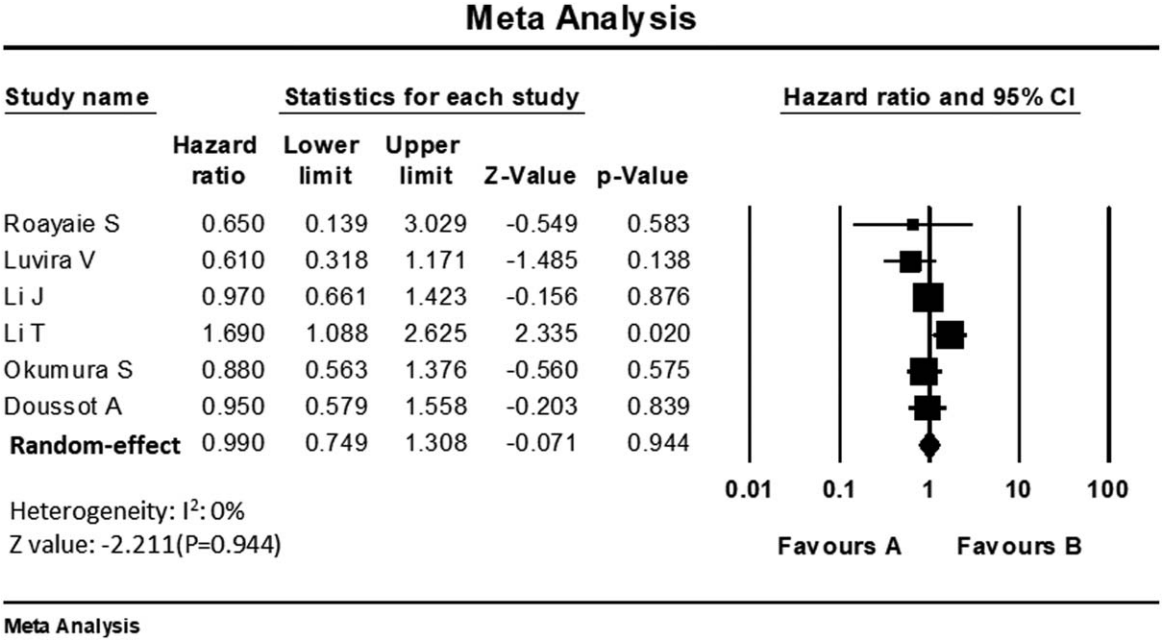

Figure 8. Forest plot illustrating the effect of adjuvant chemotherapy on disease free survival.

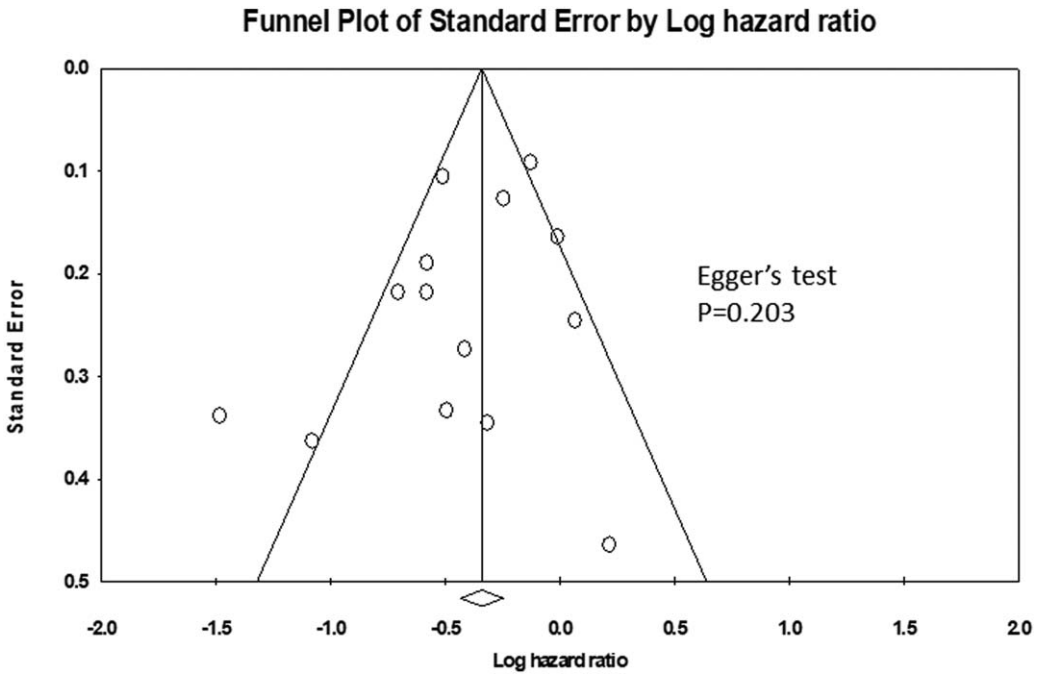

Figure 9. Funnel plot of the included studies.

landmark paper from Valle et al (ABC-02 trial) suggested that combination of gemcitabine with platinum group cytotoxic agents provides better oncological control than gemcitabine alone in locally advanced or metastatic biliary tract cancer.[40] The role of this gemcitabine-platinum base chemotherapeutic regimen in the context of adjuvant treatment has yet to be defined. We demonstrated a protective effect in patients using gemcitabine base chemotherapy over surgery alone group (Fig. 7); however, heterogeneity could be substantial among the studies used in this subgroup analysis, that is, gemcitabine alone or in combination with platinum or non-platinum cytotoxic agents, route of drug administration, dosage, and duration are some of the potential confounders). A randomized controlled trial with well-designed patient enrolment and treatment protocol is eagerly awaited to further clarify this issue.

Table 3

NOS of the included studies.

Study	Selection	Comparability	Outcome	Total
Roayaie S[21]	**	*	*	4
Bhudhisawasdi V[30]	***	*	***	7
Wu ZF[25]	****	**	**	8
Ribero D[19]	****	*	**	7
Luvira V[29]	**	*	*	4
Dhanasekaran R[23]	**	*	*	4
Miura JT[20]	***	**	*	6
Liu R[28]	**	*	*	4
Li J[26]	***	*	**	6
Li T[27]	****	*	**	7
Kim DH[33]	**	*	*	4
Okumura S[31]	***	**	**	7
Schweitzer N[32]	****	**	**	8
Doussot A[22]	****	*	**	7
Reames BN	****	**	**	8

NOS = Newcastle–Ottawa Score.

Concerning the efficacy of different routes of chemotherapy administration, there has been no direct comparison between systemic intravenous and TACE in the literature. From our subgroup analyses, clear survival benefit of using systemic intravenous adjuvant chemotherapy was demonstrated (HR 0.627, 0.491–0.799, $P < .001$). On the contrary, no significant benefit in overall survival could be shown in the TACE subgroup (HR 0.679, 0.313–1.469, $P = .325$). The authors were more in favour of systemic intravenous as the route of adjuvant chemotherapy administration, since majority of the ICC recurrences are extra-hepatic; Regional nodal basins, peritoneum, lung, and bones are common sites of treatment failure, and systemic adjuvant treatment should be a better option to eradicate small metastatic foci in these areas. In addition, TACE induces tissue hypoxia by blocking hepatic artery, this promotes neo-vascularization and possibly facilitates the spread of any residual ICC cells;[41–44] these issue is particularly of concern in patients who had close resection margin. Nonetheless, TACE is associated with good side-effect profile and is well-tolerated by over 80% of the patients,[45,46] it could still be an option for patients with marginal physiological reserve and poor tolerance to systemic chemotherapy before further evidence emerged.

Studies investigating the effect of adjuvant chemotherapy on disease-free survival were scarce. This is probably related to the fact that ICC patients usually have a limited disease-free survival even after curative hepatectomy making it difficult to demonstrate any treatment effect with small case number. Among the 6 studies (Fig. 8) that presented the effect of adjuvant chemotherapy on disease-free survival, 5 of them showed no significant benefit. Study from Li et al[27] was the only 1 which demonstrated a "bi-polar" effect in the use of adjuvant TACE for ICC patients (i.e., adjuvant TACE was associated with benefit in overall survival but at the same time leading to an inferior disease-free survival). According to the explanation from Li et al, this was partly related to patient selection (i.e., TACE tends to benefit more in patients with advanced disease), and partly related to the 2 effects associated

with TACE; Embolization of the hepatic artery leads to growth factor release from ischemic tissue favours local recurrence while chemotherapeutic agents dissipated in the hepatic parenchyma helps to suppress the growth of any recurrent tumor.

There were some limitations in the current analysis; first, majority of the studies included were single center retrospective series, some studies did not present data about margin and nodal status and this might weaken the power of the meta-analysis. Inclusion of qualitative assessment (i.e., the NOS system) for each study helps readers to understand the nature of the studies. Second. Toxicity from adjuvant chemotherapy was not analyzed, as this information were not available in most of the included series, a separate study focusing on the severity and incidence of toxic effect would help to address this problem. In addition, the proportion of ICC patient who received concurrent or sequential external radiation was not clearly documented in most of the included study, and its effect could not be evaluated in this current analysis. The message derived from this meta-analysis should prompt future randomized controlled trial which is able to propose a generalizable treatment protocol and better quantify the anticipated oncological benefit in different patient strata.

5. Conclusion

The results from this meta-analysis suggested that adjuvant chemotherapy are associated with improved overall survival and should be offered to ICC patients following curative hepatectomy, in particular, those who had more advanced disease. Systemic intravenous route of chemotherapy administration with the use gemcitabine base regimen are the preferred approach.

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